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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/023,182	12/17/2001	Elisabeth Stockert	LUD-5466.7 DIV	3379

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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 10/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/023,182	**Applicant(s)** STOCKERT ET AL.	
	Examiner MINH-TAM DAVIS	**Art Unit** 1642	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 03 August 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☒ Applicant's reply has overcome the following rejection(s): 102 rejectioin .
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: *41*.
   Claim(s) rejected: *32,34-37 and 40*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see attached .
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Accordingly, claims 32, 34-37, 40-41 are being examined.

The following are the remaining rejections.

OBJECTION

Claim 41 remains objected to as being dependent upon rejected base claims, but would be allowable if rewritten in independent forms.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

Rejection under 35 USC 112, first paragraph of claims 32, 34-37,40 pertaining to lack of a clear written description of an immunoreactive portion that is processed by a cell to from a peptide which complexes to an MHC molecule and provides a T cell response, remains for reasons already of record in paper of 06/03/05.

Applicant argues that peptides which are proven to be T cell stimulators and full within the scope of the claims of the invention are known and is of record.

Applicant argues all claimed molecules share the structural requirement of having an amino acid sequence encoded by SEQ ID NO:1.

Applicant recites Example 14 of the written description, in which a claim, drawn to a protein of SEQ ID NO:3 and variants thereof that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A to B, meets the written description requirement,

even though only one specific species is identified, in view of the disclosure of an assay for determining if the catalytic activity is present.

Applicant argues that three functional species are identified in the instant application, and no variation from a reference molecule is permitted. Applicant argues that further, an assay is described, which the USPTO confirms is one that is usable.

Applicant argues that with respect to the data submitted, the specific peptides disclosed in the art are disclosed in the specification, because these are peptides consisting of amino acid sequences encoded by SEQ ID NO:1.

Applicant's arguments in paper of 08/03/05 have been considered but are found not to be persuasive for the following reasons:

A. It is noted that **at the time the invention was filed**, only three peptides consisting of SEQ ID Nos:4-6, which are fragments of the full length amino acid sequence encoded by the polynucleotide consisting of SEQ ID NO:1, and which complex with an MHC molecule and provide a T cell response, were disclosed.

The claims, however, encompass a genus of peptides, besides SEQ ID Nos:4-6, which are certain specific fragments of the amino acid sequence encoded by SEQ ID NO:1, wherein said specific fragments have the specific properties of complexing with an MHC molecule and providing a T cell response.

However, except for SEQ ID Nos:4-6, the structure of other peptides of the claimed genus of peptides are not disclosed at the time the invention was made.

Further, it is noted that immunoreactive portion reads on linear and conformational B cell and T cell epitopes. Herbert et al. (The Dictionary of Immunology,

Academic Press, 4th edition, 1995, p.58, of record) define epitopes as the region on an antigen molecule to which antibody or the T cell receptor binds specifically wherein the 3-dimensional structure of the protein molecule may be essential for antibody binding. However, the specification fails to disclose sufficient guidance and objective evidence as to the linear and or three-dimensional conformation of the polypeptide fragments which constitute epitopes recognized by B cell or T cell receptors the claimed invention. Moreover, as evidenced by Greenspan et al, of record, defining epitopes is not as easy as it seems (Nature Biotechnology 7:936-937 (1999). Even when the epitope is defined, in terms of the spatial organization of residues making contact with ligand, then a structural characterization of the molecular interface for binding is necessary to define the boundaries of the epitope (page 937, 2nd column).

However, the specification has not identified which immunoreactive portions of the peptide encoded by the cDNA fragment of SEQ ID NO:1 have essential characteristics of the claimed linear and conformational B cell and T cell epitopes, other than the three linear peptides of SEQ ID NO:4, 5, 6 that elicit CTL response.

It is noted that not any peptides of an amino acid sequence could bind to an MHC molecule and provide a T cell response. It is well known in the art that antigen peptides have to fit into and binds to B cell antigen receptors, which are immunoglobulins on B cell surface for activation of B cells (Stites et al, 1997, Medical Immunology, 9th ed, Appleton & Lange, Stamford, Connecticut, figure 3-9 on page 51, pages 50-51, 118-119, of record). It is also well known in the art that T cell receptors recognize the ligands comprising peptide antigens that are bound to MHC molecules,

and that individual T cells respond only to a specific combination of antigen and MHC (Stites et al, supra, page 130). In other words, peptides that are expected to bind to MHC molecules, such as those disclosed in the specification are not necessary ligands of T cell receptors, wherein said ligands provide a T cell response, because T cell receptors have to recognize a specific combination of antigen and MHC, and thus the specification does not provide adequate examples of the claimed T cell epitopes that invokes a T cell response, by providing examples of peptides that are expected to bind to MHC molecules. This is clearly shown by the teaching of Kirkin et al, of record, that only few peptides from melanoma associated antigens have been so far identified as being recognized by specific CTLs, and that some Melan-A/MART-1 peptides although having high affinity for HLA-A2.1 antigen do not induce the generation of melanoma specific CTLs in vitro.

Although all the claimed peptides or immunoreactive portions share the structural requirement of having to have an amino acid sequence encoded by SEQ ID NO:1, i.e. they have to be fragments of the amino acid sequence encoded by SEQ ID NO:1, **the claimed peptides, including SEQ ID Nos: 4-6, do not share the same common structure**, because different fragments of a protein do not necessarily have similar amino acid composition, as shown clearly, for example, by different structure or amino acid compositions of SEQ ID Nos:4-6, and of the peptides disclosed after the invention was made, as submitted by Applicant in the response of 04/01/05.

Moreover, Example 14 is not applicable to the instant application, because the variants in Example 14 at least share 95% sequence identity with SEQ ID NO:3, and sharing the same well known function.

In the instant application, the limitation of sharing 95% sequence identity, or sharing a common structure, is not disclosed in the claims, or the specification. There is no disclosure of a common structure that correlates with the ability to complex with an MHC molecule and elicit a T cell response.

Concerning Applicant's language "no variation from a reference molecule is permitted", it is not clear which reference molecule is referred to. If the reference molecule is the protein encoded by SEQ ID NO:1, no variation from the protein encoded by the SEQ ID NO:1 only means that the claimed peptides have to be a fragment of said protein.

Thus, although the 3 species, the peptides consisting of SEQ ID Nos:4-6, are disclosed, the claimed invention does not meet the 112, first paragraph, written description requirement, as shown by the standards in the example of Lilly, because of the following reasons:

1) There is **no correlation between structure and function for the claimed immunoreactive portions, because there is no disclosure of a common structure that correlates with the ability to complex with an MHC molecule and elicit a T cell response.**

2) **SEQ ID Nos:4-6 are not representative species**, because there is no common structure among SEQ ID Nos:4-6.

Thus, one of skill in the art would reasonably conclude that Applicant did not have possession of the claimed immunoreactive portions having the properties of binding to MHC molecule and providing a T cell response at the time of filing.

B. Concerning Applicant's arguments that a number of T cell epitopes, found post-filing, in the protein encoded by SEQ ID NO:1, are disclosed in the specification, because these are peptides that consist of amino acid sequences encoded by SEQ ID NO:1, this is not found to be persuasive.

It is noted that the amino acid sequence consisting of the specific peptides cited in the post-filing references are specific fragments of the amino acid sequence encoded by SEQ ID NO:1, wherein said specific fragments, but not any fragments of said amino acid sequence encoded by SEQ ID NO:1, have the specific properties of binding to MHC molecule and providing a T cell response.

Contrary to Applicant arguments, although the specification discloses the amino acid sequence encoded by SEQ ID NO:1, however, except for the peptides of SEQ ID NO:4-6, which other peptide fragments that have the specific properties of binding to MHC molecule and providing a T cell response are not disclosed in the specification. It is noted that peptides consisting of amino acid sequences encoded by SEQ ID NO:1 are only generic , because not any peptides of a full length amino acid sequence would have the specific properties of binding to MHC molecule and providing a T cell response, supra.

Applicant however claims specific subgenus of fragments of the amino acid sequence encoded by SEQ ID NO:1, having the specific properties of binding to MHC molecule and providing a T cell response.

Thus, one of skill in the art would reasonably conclude that Applicant did not have possession of the claimed immunoreactive portions having the properties of binding to MHC molecule and providing a T cell response at the time of filing.

In conclusion, the claimed invention does not meet the 112, first paragraph, written description requirement.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JEFFREY SIEW can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MTam Dis
09/29/05

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER
9/29/05